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Based on Studies of the Respiration, Urine and Blood

ELLIOTT P. JOSLIN, M.D.
BOSTON

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CARBOHYDRATE UTILIZATION IN DIABETES

BASED ON STUDIES OF THE RESPIRATION, URINE AND BLOOD *

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In the classical work of Naunyn[1] on diabetes mellitus occurs the following passage: "In general, even in severe diabetes, at least in man, the carbohydrates ingested are not completely excreted in the urine again as sugar. A portion of the starch, as well as of the dextrose, will be burned in the organism." This view was also shared by Kulz. Naunyn, however, refers to a case in which von Mering records an excretion of all the sugar ingested, and attention is called in the report of the cases of Kulz to four instances in which apparently a similar condition existed.

Von Noorden[2] defines diabetes as "a disease in which the capability of the organism adequately to burn grape sugar is pathologically lowered," and in another place[3] he says: "One cannot help thinking that, in man, even when death has resulted from coma, the diabetes has not always been 'quite complete'—that is to say, the pathological processes which produce diabetes have not developed so far, and the factors which favor the storing up of glycogen have not been so completely destroyed as is the case in a dog whose pancreas has been entirely ablated."

Notwithstanding all the work on diabetes, this question of the utilization of carbohydrates in human diabetes has not been settled. In diabetic dogs evidence has accumulated pointing to the complete loss of this power to utilize carbohydrate, and the work of Murlin and

* From the Nutrition Laboratory of the Carnegie Institution of Washington, Boston.

* I wish to acknowledge my grateful appreciation of the help received from Mr. Emmes, Miss Babcock, Miss Tompkins, Miss Corson and Miss Sandiford of the Nutrition Laboratory, as also my indebtedness to Mr. Higgins, who controlled several of the experiments with the Tissot apparatus, and to my secretary, Miss Helen Leonard, for cheerful work on long computations and puzzling charts.

1. Naunyn: Der Diabetes Melitus, 1906, p. 173.
2. Von Noorden: Zuckerkrankheit, Ed. 6, 1912, p. 2.
3. Von Noorden: Metabolism and Practical Medicine, 1907, iii, 542.

Cramer[4] has given definite results on this point, although so recent a writer as Landsberg,[5] working from a different point of view with other animals, comes to the opposite conclusion. The present paper is concerned with diabetes in man and I wish to call attention to certain observations bearing on this problem which are related to the body weight, the urine, the storage of carbohydrate in the body, the respiratory metabolism of diabetics both fasting and following the administration of food and the remarkable disappearance of acidosis in diabetics with prolonged fasting, which is associated with a rise in their respiratory quotient.

I. THE INFLUENCE OF WEIGHT ON THE DETERMINATION OF THE UTILIZATION OF CARBOHYDRATES IN DIABETES

The changes in weight which occur in a normal individual, following a slight increase of the carbohydrate in the diet, are so striking that one might hastily conclude that a study of the weights of a diabetic patient would give some idea as to his utilization of starch and sugar. A closer scrutiny of the problem, however, reveals many difficulties. In the first place, the diet employed in most cases of diabetes and all severe cases, is low in carbohydrates, and seldom reaches 10 per cent. of that of normal individuals. In other words, it amounts to less than 50 gm. carbohydrate—200 calories—per day. The effect of 200 calories on the weight is possible of determination theoretically, but practically such an experiment is difficult because the protein, fat and carbohydrate must be kept at uniform levels for a long period. But in a severe case of diabetes some of even this small amount is lost in the urine, which renders the available carbohydrate for increasing the weight still less. There are other complications. In a severe case of diabetes, the patient with 50 gm. of carbohydrate in the diet, usually excretes more than 50 gm. of sugar in the urine, and it is difficult to assign in proper proportion this excess of urinary sugar between the carbohydrate ingested and the carbohydrate already stored in the body on the one hand, and the protein simultaneously ingested and the body protein on the other.

Remarkable changes in the weight of normal as well as of diabetic patients will also occur, although the caloric value of the diet remains constant, if the proportion of fat to carbohydrate is altered. A diet rich in carbohydrate brings about an increase in weight, whereas a diet of exactly the same number of calories, although chiefly made up of fat, lowers the weight. These changes undoubtedly are due simply

4. Murlin and Cramer: Jour. Biol. Chem., 1913, xv, 365.
5. Landsberg: Deutsch. Arch. f. klin. Med., 1914, cxv, 465.

to the retention of water by the tissues on a carbohydrate diet, and loss of water on a fat diet. Such changes appear reasonable because the storage of 1 gm. of carbohydrate in the body demands the retention of 3 gm. of water, 1 gm. of protein requires the storage of 0.75 gm. of water, and 1 gm. of fat requires only 0.1 gm. of water. These changes are well illustrated[6] by Table 1.

TABLE 1.—Changes in Weight Under Fat and Carbohydrate Diets

Date	Food and Drink			Body Weight kilos	Gain (+) or Loss (—) gm.
	Solid Matter gm.	Water gm.	Total gm.		
Carbohydrate Diet					
4/16/04	...			75.086	
4/16-17/04	970	3,577	4,547	75.443	+ 357
4/17-18/04	966	3,553	4,519	75.414	— 29
4/18-19/04	966	3,491	4,457	75.269	— 145
Fat Diet					
4/19-20/04	750	3,108	3,859	74.319	— 950
4/20-21/04	745	4,150	4,896	73.480	— 839
4/21-22/04	747	4,152	4,899	72.528	— 952

Average gain per day, carbohydrate diet, + 61 gm.
Average loss per day, fat diet, — 914 gm.
Water stored per day, carbohydrate period, + 165 gm.
Water lost per day, fat period, — 906 gm.

It is important for the clinician to bear this in mind, because it explains the rapid change in weight which often follows the initial diminution of the carbohydrate in the diet of diabetic patients and its replacement with fat.

An increase in weight following a marked increase of carbohydrate in the diet is strikingly illustrated in severe diabetic patients under the oatmeal treatment.[7] Under these conditions the weight may rise 4.5 kg. in one or two days. Undoubtedly you all have seen edema during the course of an oatmeal cure. It is significant that some of these cases show little or no carbohydrate in the urine. I cannot give proof that patients showing this increase in weight fail to give evidence of burning more than a trifling amount of carbohydrate, but from other similar cases I suspect this often to be the case. This point deserves further study. I think, however, that there will be general agreement that the gain in weight following the sudden introduction of large quantities of carbohydrate is accounted for by the storage—temporarily, perhaps—of carbohydrate in the body. That this storage or delay of excretion is accentuated in the presence of diseased kidneys

6. Benedict and Joslin: A Study of Metabolism in Severe Diabetes, Carnegie Institute of Washington, 1912, Pub. No. 176, p. 93.
7. Mirowsky: Deutsch. med. Wchnschr., 1912, xxxviii, 459.

is common knowledge. Barrenscheen[8] showed that milk sugar excretion was delayed on the day following an oatmeal cure.

The administration of sodium bicarbonate is frequently followed by a gain in weight. Thus,[9] in Case 220, the changes in weight during the administration of sodium bicarbonate were as shown in Table 2.

TABLE 2.—Changes in Weight During the Administration of Sodium Bicarbonate

Date	Sodium Bicarbonate gm.	Body Weight kilos.	Date	Sodium Bicarbonate gm.	Body Weight kilos.
11/2	0	48.1	11/ 7	20	50.7
11/3	0	48.6	11/ 8	20	51.5
11/4	0	49.0	11/ 9	20	52.4
11/5	0	48.6	11/10	20	53.3
11/6	20	49.3	11/11	20	53.3

In order to show that this gain in weight was not directly due to the alkali, but rather to retention of salt, the weights of another diabetic patient, Case 135, were taken while on a salt-free diet[10] (Table 3).

TABLE 3.—Changes in Weight on a Salt-Free Diet

	Intake						Urine								
Date, 1908	$NaHCO_3$ Gm.	Carb., Gm.	Protein, Gm.	Fat, Gm.	Alcohol, Gm.	Liquids c.c.	Vol., c.c.	N, Gm.	NH_3, Gm.	Acetone and Diacetic Acid., Gm.	Beta-oxy. Acid, Gm.	P_2O_5, Gm.	Cl., Gm.	Sugar, Gm.	W Lb
1/26	0	135	110	185	..	3,500	3,720	21.8	4.2	7.9	29	4.4	8.2	160	88
1/27	0	135	110	185	..	3,500	3,940	19.6	4.3	7.8	29	4.5	6.3	165	89
1/28	0	135	110	185	..	3,500	3,210	20.5	4.4	7.3	24	4.6	5.9	160	86
1/29	0	135	90	155	..	3,500	3,210	19.2	4.1	7.3	26	4.2	4.8	163	85
1/30	25	135	70	185	..	3,500	3,190	16.3	3.5	8.7	33	4.1	1.6	146	85
1/31	25	120	60	95	23	5,370	4,600	19.1	4.3	12.6	51	5.1	2.3	146	83
2/1	37	130	100	130	45	5,250	4,050	18.7	3.3	10.7	39	4.3	2.0	137	82
2/2	52	70	60	95	45	5,370	3,510	16.0	3.5	10.2	37	3.9	2.1	121	81
2/3	..	15	15	30	45	800	360	15.0	...		..	...	...	86	..

It will be seen that while on the salt-free diet the weight steadily fell, and despite the administration of sodium bicarbonate later, no increase in weight occurred. This observation has been elsewhere confirmed. I might here make the clinical observation that a salt-free diet in diabetes is inadvisable. It is also interesting that I have never

8. Barrenscheen: Biochem. Ztschr., 1912, xxxix, 232.
9. Benedict and Joslin: Loc. cit. (Note 6) p. 94.
10. Joslin and Goodall: Jour. Am. Med. Assn., 1908, li, 727.

seen the death from diabetic coma of a diabetic patient who had dropsy, nor have I encountered such in the literature.

The simple enumeration of these various facts affecting the weight shows how complicated is the determination of the utilization of carbohydrate from it alone. Changes in weight, however, do afford, when combined with other methods of clinical investigation, new fields for work.

The changes in weight which a healthy fasting man undergoes at the beginning of a fast are known. The fasting man at the Nutrition Laboratory lost 2,850 gm. in three days, and consumed during these three days body substance equivalent to 161 gm. of protein, 149 gm. of carbohydrate and 407 gm. of fat. It is possible that from a series of observations on diabetic patients similarly fasted, conclusions of value as to the storage of carbohydrate in the body might be secured. Ten of my patients who were available for this purpose showed on an initial fast a loss of weight considerably less, and occasionally a gain in weight was recorded. Following the termination of the fast, although very little food was given, an increase in weight out of proportion to the amount of food given was almost invariably observed.

In one case no mineral waters or alkalies were taken, and yet gain in weight occurred during fasting. It is not unexpected that the gain in weight was often coincident with a fall in the excretion of urine. A gain in weight during fasting raises the question as to whether new carbohydrate has not been formed in the body, and as a result of its formation water retained. This line of investigation deserves attention. It will be referred to later in the discussion of severe cases of diabetes treated by prolonged fasting, the method which Dr. F. M. Allen[11] has had the courage to introduce and has so accurately defined that it is safe for any practitioner to employ.

II. THE UTILIZATION OF CARBOHYDRATES BASED ON INTAKE IN DIET AND OUTGO IN URINE

The comparison between the carbohydrate ingested and the sugar excreted in the urine is the common method of determining the utilization of carbohydrates. It would appear to be a simple procedure, but, as a matter of fact, the problem is far more difficult than has heretofore been considered. Your attention is first directed to the possibilities of error in reckoning the carbohydrate in the diet. Most severe diabetics under careful observation live on diets low in carbohydrate, seldom in excess of 50 gm. Therefore errors of 5 gm. in the estimation of

11. Allen: Jour. Am. Med. Assn., 1914, lxiii, 939; Boston Med. and Surg. Jour., 1915, clxxv, 241.

carbohydrates, though actually small, are proportionately large. It is seldom that the actual quantity of carbohydrate in the diet has been analyzed. In many of the cases food has not even been carefully weighed, and approximate portions of food have been supposed to contain definite quantities of carbohydrate. Take, for example, cream: The quantity of carbohydrate contained in half a pint may vary 5 gm., making an error of 10 per cent., if the total carbohydrate for the day amounted to 50 gm., or 20 per cent. if limited to 25 grams.

Vegetables constitute a considerable proportion of the diet of these patients with severe diabetes. Often in the literature—and I plead guilty to the charge—the quantity of carbohydrate in the mixture of vegetables chosen from those containing less than 10 per cent. carbohydrate for the day, has been roughly estimated. Recently I have taken more careful account of the amount of vegatables eaten, and it has come out that the quantity of vegetables prescribed and eaten frequently varies from 300 gm. to 1,000 gm. Any accurate computation, therefore, of a carbohydrate balance must be based not alone on the total quantity of vegetables eaten in the day, but on the actual quantity of each vegetable, even in these low carbohydrate groups. Furthermore, varieties of the same vegetable vary in percentage of carbohydrate. It makes a difference of 5 gm. in a day whether 500 gm. vegetables contain 1 per cent. more or less of carbohydrate. But this is not all. Analyses of carbohydrate in vegetables include the cellulose contained in them as well as the starch and sugar. How much shall we subtract from our total carbohydrate intake on account of this undigested cellulose which is lost in the feces?

The other foods commonly used in the study of the metabolism of diabetic patients are potato, oatmeal, bread, fruit. The potato, oatmeal and bread are usually carefully weighed, and the analyses of these foods are fairly constant, but the percentage of carbohydrate is so large that I should not dare to be positive about the quantity of carbohydrate which my patient received unless standard varieties of these foods were employed. With fruit frequent errors exist, because usually an orange or grapefruit is allowed and seldom the actual weights of the portions eaten are determined. A further error occurs in that the intake of carbohydrate is reckoned indifferently as starch or sugar. As a matter of fact, 100 gm. of starch when converted to sugar amount to 105 gm. Errors of 5 and 10 gm. a day in computing the carbohydrate intake may easily occur and in a period of a week form notable amounts, from 35 to 70 gm. Physiologists and physicians must not take too seriously clinical statements about the carbohydrate in the diet, and greater accuracy must be employed in the future. We need, first, a standard test diabetic diet, and, second, we need to

employ it for at least five days. Unfortunately, even at the end of this time the results may be unsatisfactory, because the condition of the patient's tolerance may have changed in this period either for better or worse.

The estimation of sugar in the urine is far more accurate than that of the carbohydrate in the diet, provided the analysis is made in one of our best laboratories, but I would hesitate to accept as final in accurate computations many routine analyses made in private practice or in hospitals. Too often the method employed in the estimation of the sugar is not mentioned, and I suspect many results are obtained with the polariscope which may involve an error of 20 gm. or more, owing to the presence of levorotary bodies. Urinary analyses, however, are usually far and away ahead in accuracy of that observed in the collection and measurement of the urines of diabetic patients. The admirable methods adopted in the ward of the Russell Sage Institute at Bellevue Hospital and at the Rockefeller Hospital have been seldom followed by experimenters in the past. I pass over errors of forgetfulness or design on the part of the patients, as regards both diet and collection of urine. Dogs may not be any more honest, but we do not expose them to temptation or trust their memory. How often a patient states that a trifling amount of urine has been lost at stool! I realize this is trite, but a good share of the arguments based on the utilization of carbohydrate rests on data which are not above reproach.

The variability of excretion of urine and urinary constituents from day to day is another source of error. If the diet is not constant the variation may be great. In one of our tests designed to determine the utilization of levulose, during seven days prior to the administration of levulose the average volume of urine was 1,079 c.c. On the day the levulose was given the volume of urine was 966 c.c., the next day 390 c.c., and on the following day it amounted to 1,175 c.c.; it then returned to near the average quantity. Yet the habits of this patient's daily life were nearly constant, and except for the one levulose day changes in the diet were not extreme. Such marked variations in the volume of the urine on successive days must be reckoned with, because with such great changes in volumes of urine, the quantities of the constituents of the urine change too, though to a much less extent. In this same case, the average daily excretion of nitrogen for the fifty-five days which included this period was 7.3 gm., but on the day when 81 gm. levulose were given with very little other food, it fell to 6.53 gm. and on the next day to 4.34 gm. This low point was never reached by this same patient on a fasting day, and the quantity of levulose is considerably less than would be supposed to exert so strong a positive action, particularly when delayed or diminished oxidation

is taken into consideration. Consult Table 4 and also chart of variations in excretion of urine and sugar of a severe diabetic on a constant diet, shown further on.

TABLE 4.—Effect of Levulose

Case 785. Male, aged 17. Weight, 42 Kilos.

Output					Intake				
Vol., c.c.	Diac. Acid	Sugar, Gm.	Nitrogen, Gm.	Ammonia, Gm.	Carb., Gm.	Prot., Gm.	Fat, Gm.	Alcohol, Gm.	Calories
1,079*	+	11.1†	7.83		17	58	127	9	1,506
966	+	7	6.53	0.69	90‡	21	30±	3	735
390	++	5	4.34	0.35	20	63	110	9	1,385
1,175	+	3	8.35	0.74	20±	63	110±	9	1,385±

* Average for previous seven days.
† None on six days.
‡ Levulose, 81 gm. Carb. in Diet 9 ± gm. in the form of vegetables.

Experiments designed to test the utilization of carbohydrate should be conducted on patients who are in equilibrium both as regards weight and urinary excretion.

III. THE IMPORTANCE AS WELL AS THE INFLUENCE OF CARBOHYDRATE STORED IN THE BODY ON THE UTIILIZATION OF CARBOHYDRATE INGESTED

It is well known that following a period of fasting large quantities of carbohydrate can be administered without subsequently appearing in the urine. The best illustration of this is von Noorden's oatmeal treatment. Thus Case R. of the Benedict and Joslin series[12] showed a positive carbohydrate balance of 520 gm. during an oatmeal cure, although he never after this cure became sugar-free save for occasional days, despite rigorous dieting. A more spectacular demonstration is the severe diabetic of Klemperer,[13] who took 100 gm. of glucose in divided portions during twenty-four hours without more than a few grams appearing in the urine. Almost as striking is that of a boy of 17 (Case 785) who came to me in the twentieth month of the disease. By consulting Table 4 it will be seen that only 7 gm. of sugar appeared in the urine following an intake at one time of 81 gm. levulose, although by observations before and after the tolerance was known to be low. A summary of his metabolism is given in Table 5.

12. Benedict and Joslin: Loc. cit. (Note 6) p. 57.
13. Klemperer: Therap. d. Gegenw., 1911, lii, 447.

TABLE 5.—Summary of Metabolism in Case Shown in Table 4*

Case 785. Severe diabetes. Weight, 42 kilos. Male. Age at onset, 15. Duration since onset twenty months.

Period	Nitrogen Balance		Carbohydrate Balance	
	Urine and Feces	Diet	Urine	Diet
55 days	440.	407.	190.	919.
Daily average	8.0	7.0	3.5	16.7
Daily average	8.9	Sugar present in urine 20 days		15.4
		7.8	8.8	
Daily average	7.5	Sugar absent from urine 32 days		15.1
		6.4	0.0	

* Nitrogen in feces estimated at 10 per cent. of nitrogen in diet.

During the fifty-five days he was under my observation the average daily nitrogen in the diet was estimated at 7.0 gm., and in the urine and feces 8.0 gm. The carbohydrate in the diet was 16.7 gm. and in the urine 3.5 gm. During thirty-two of the fifty-five days, sugar was absent from the urine and on twenty days it was present, although the average daily carbohydrate in the diet was the same. A study of Table 5 would suggest this being due to the slightly lower nitrogen intake on the sugar-free days. This is not quite justifiable, because another factor enters in—namely, starvation—for on several of the thirty-two days the patient received no food at all. These starvation days evidently played an important rôle. How very important is shown by the test already recorded in Table 4, where 81 gm. of levulose were administered and only 7 gm. carbohydrate appeared in the urine.

Is it possible for the body to store so large a quantity of carbohydrate as 520 or even more grams? Furthermore in what form may it be retained in diabetic patients?

Nearly all experiments on the utilization of carbohydrates in the past have been based on the difference between the carbohydrate intake and the carbohydrate excreted. Unless the amount of the carbohydrate stored in the body is known, it is unjustifiable to say that the carbohydrate excreted represents a part of that ingested during the same twenty-four hours. All data in reference to the D:N ratio are confused by the possibility of stored carbohydrate. The importance of the storage of carbohydrate thus becomes evident.

The influence of carbohydrate so stored in the body is also great. Whatever virtue the oatmeal cure possesses, all agree that it depends

in major part on preceding starvation, which has tended to exhaust the carbohydrate depots of the body.

Glycogen.—Carbohydrate is stored in the body in various ways but most of it is supposed to be in the form of glycogen, and this is about equally divided between the liver and the muscles. An old estimate of Bunge that the body had 400 gm. is roughly approximated by experiments on fasting men and professional athletes doing severe work without food. This figure may be taken as a fair average, but there are enormous variations. This statement is based on glycogen which has been shown to be burned; it does not exclude the possibility of some glycogen still remaining in the body, and in fact Benedict says: "It would appear that the estimate of 400 gm. of glycogen for the content of the body is if anything too small rather than too large." Experiments on fasting men show that they may burn from 93 to 232 gm. in the first three days.[14, 15] In diabetic patients the quantity of glycogen is universally considered to be far below this amount, but Frerichs[16] found, on puncturing the liver of two diabetics, a small amount of glycogen in one and a considerable amount in the other, and Kulz[17] found from 10 to 12 gm. glycogen in the liver of a diabetic who had been for a long time on a diabetic diet. Examinations of the tissue removed from the livers of living diabetic patients show appreciable quantities of glycogen, and it is the experience of pathologists that the organs of diabetic patients contain more than traces of glycogen. It is most unfortunate that no data exist which enable us to determine what this minimum is. It is quite conceivable that although it might be extremely small at any one moment, a small quantity might be frequently formed and destroyed, and the sum of these small quantities reach a substantial amount in twenty-four hours.

The recent work of Helly[18] throws new light on the problem. He points out the striking contrast between the constant presence of glycogen in the liver of human diabetes and the very small quantity which is found in the severe diabetes of depancreatized dogs, yet even in the latter the power of the liver to form or deposit glycogen is shown when levulose is administered. If a milder form of diabetes is produced in the dog more glycogen remains in the body and there is a closer resemblance to human diabetes; whereas with total removal of the pancreas there was only 0.065 per cent. of glycogen in the liver.

14. Benedict: The Influence of Inanition on Metabolism, Carnegie Institute of Washington, 1907, Pub. 77, p. 464.

15. Benedict: A Study of Prolonged Fasting, Carnegie Institute of Washington, 1915, Pub. 203, p. 251.

16. Frerichs: Ueber den Diabetes, p. 272; cited by Nehring and Schmoll (Note 34).

17. Kulz: Arch. f. d. ges. Physiol. (Pflüger's), 1876, xiii, 267.

18. Helly: Ztschr. f. exper. Path. u. Therap., 1914, xv, 464.

On the other hand, with partial removal, even though there be 8 to 10 per cent. of sugar in the urine, there was 0.3 per cent. of glycogen. By microscopic examination so considerable a quantity as this appeared small.

Blood Sugar.—Sugar is also stored in the body in the form of blood sugar. The normal quantity of sugar in the blood of healthy individuals varies between 0.07 and 0.11 per cent. and for convenience in calculations may be considered 0.1 per cent. This rises quickly after a meal rich in carbohydrates, but soon falls to its former level. In fifty-five observations on fifteen of our diabetic patients the percentage of blood sugar varied from 0.12 to 0.36 per cent. But the blood of these diabetic patients does not behave like that of normal individuals following the ingestion of food. It is true that the percentage of sugar rapidly increases following a carbohydrate meal, but it does not as rapidly fall, and in my own experience most diabetic patients, even after prolonged fasting, show values for blood sugar which are far above normal. Certain types of diabetic patients—namely, those with disease of the kidneys—are especially prone to maintain high percentages of sugar in the blood for many days after their urines have become sugar-free. It is impracticable to consider that the percentage of blood sugar is maintained independently of the other tissues in the body—first, because the percentage is so unstable; second, because there is no constant relation between the sugar in the blood serum and the sugar in the total blood, and third, because the capacity of the blood for storage of sugar is so slight. If we assume an individual of 70 kilos body weight and consider that 7 per cent. of the weight is made up of blood, we have 4.9 kilos of blood with a normal sugar content of 0.1 per cent. This would amount to 4.9 gm., even taking the highest for the normal individual, and should we take the highest figures we have encountered even after the administration of food with our diabetic patients, namely 0.36 per cent., the total quantity of sugar stored in the blood would not be far from 18 gm.—a trifle more than a half ounce.

Falta[19] has called attention to the slow return of the blood of diabetic patients to its former sugar level, and emphasizes this point as of fundamental importance in diabetes. He points out that the disturbance of blood sugar utilization is not the same as the disturbance of glycogen formation for the blood sugar regulation may be interfered with when the glycogen formation is not.

Kleiner and Meltzer[20] have also beautifully shown this same difference in depancreatized dogs. Whereas, following the injection of

19. Falta: Med. Klin., 1914, x, 9.
20. Kleiner and Meltzer: Proc. Soc. for Exper. Biol. and Med., 1914, xii, 58.

4 gm. dextrose per kilo weight, the sugar in the blood of normal dogs increases fourfold—namely, from 0.20 per cent., to 0.79 per cent.—and that of depancreatized dogs threefold—from 0.38 per cent. before to 1.19 per cent. after the injection—the blood sugar of the former returned nearly to normal at the end of an hour and a half, while the diabetic dogs even then showed 0.86. It is significant that in these experiments the quantities of sugar excreted in the urine were practically the same. Interesting as these figures are from this point of view, from another they are still more interesting. It is impossible to account for all the sugar ingested by adding together the sugar found in the blood and that in the urine. Where did the sugar go? You may say it was burned, and this possibility, though not probability, must be admitted in the normal animal, but no one would contend this to be wholly the case in the depancreatized animal.

At the Nutrition Laboratory we have been able to carry these experiments to their logical conclusion, for we have had the opportunity to determine the respiratory quotient following the administration of levulose to severe diabetics. In Table 20 will be found a report of the effect of levulose when administered to severe diabetic patients in amounts to 2.51 gm., 2.42 gm. and 1.95 gm. per kilogram body weight. In the first and third cases there was no increase in the respiratory quotient. A considerable portion of the levulose was probably excreted in the first case, but in the third little or none. The explanation of this difference in behavior in the storage of levulose is probably that the first patient had not fasted beforehand and that the third had been on a low carbohydrate diet for a long time; this is confirmed by the second case, in which also little of the levulose was excreted when administered following a period of strict dieting. An increase in the respiratory quotient occurred in this case, but it was so slight as to preclude any considerable quantity of the sugar having been burned. It should also be recorded that in all the cases the levulose was given at one time and not spread out through the twenty-four hours, as in Klemperer's test. This gives added emphasis to the possibility of the presence of an empty storehouse for carbohydrate in the body. I also have evidence that the gradual administration of carbohydrates is of little value, provided the body is not prepared to retain it. Following etherization a patient (Case 808), while fasting for the first twenty-four hours was sugar-free, but on the next day, although only 2 gm. carbohydrate per hour were administered, he excreted practically all of it, although formerly his tolerance amounted to 50 gm. carbohydrate.

The small amount of glycogen and the still smaller quantity of blood sugar represent an amount of carbohydrate far too low to

account for the phenomena above described in diabetes. Other sources for storage of sugar in the body must be sought, as has been emphasized by Ivar Bang. If we should assume that the percentage of sugar in the blood was the same for all the fluid in the body, certain amounts of sugar might be stored in this manner. While such an assumption is not wholly justifiable, it has some basis, for we know that sugar exists in the spinal fluid of diabetics, as well as in other fluids. In normals Dr. Jacobson tells me that he has not found it so closely to follow the blood, but the opposite was true in his cases of diabetes mellitus. It gets into the blood and cannot seem to get out. Notable percentages of sugar, not very different from those in the blood, have been found in pleuritic and ascitic fluids, and Husband found even 0.7 per cent. in the amniotic fluid. There is some doubt about its presence in sweat, but we do have a record of sweet tears. Yet granted that the assumption is correct, we cannot increase our storage capacity very much that way. For example, assuming the total quantity of fluid in the body as 60 per cent. of the body weight of 70 kg., we have 42 kg. of body fluid, from which we must deduct 4.9 kg. already reckoned as blood. This leaves us a remainder of 37.1 kg. of fluid in the body, and using the highest figure—0.36 per cent.—for blood sugar which we have encountered, the quantity of sugar in this mass of fluid would be only 133 gm. This is not enough relatively to explain Kleiner's and Meltzer's experiment.

Another source for the formation, although perhaps not for the storage of carbohydrate in the body, has long been recognized in protein. The close connection which is maintained between protein and carbohydrate in diabetes would make a clinician with modest chemical knowledge seek for some combination of carbohydrate in the protein molecule—some arrangement by which a portion of the sugar molecule could be stored in protein or given up as occasion arises, just as water is squeezed out of a sponge. Good chemists, and I have asked many, assure me that even with glucoproteins sugar can be extracted from the protein molecule only when the molecule itself is disintegrated. The large quantity of movable protein and fat in the body suggests a large carbohydrate reservoir, too. Few realize how large this quantity of movable protein is. It has been shown by Albert Müller[21] that by overfeeding, 210 gm. of nitrogen, the equivalent of 1260 gm. of body protein, in turn the equivalent of 6.3 kilos of muscle tissue, can be retained by the body, and conversely, it has been shown by Benedict[15] that even more—277 gm.—can be removed. This movable protein amounts to about one-third of the total body protein. The readiness

21. Müller: Zentralbl. f. d. Ges. Physiol. u. Path. d. Stoffswechs., 1911, vi. 617.

with which fat can be increased and decreased in the body is universally recognized.

Although we are not allowed to say that carbohydrate can be extracted from the protein molecule, leaving it intact, we do know that in severe diabetes sugar can be formed out of protein. Professor Lusk[22] has demonstrated this in completely depancreatized dogs and in his now famous diabetic patient, 3.65 gm. dextrose appeared in the urine for each gram of nitrogen therein contained. This represents approximately 60 gm. dextrose for each 100 gm. protein. If we should assume that in diabetic patients there were 1,200 gm. movable protein, this would furnish a possible source of 720 gm. more of carbohydrate.

Unfortunately one cannot be sure that in the disintegration of the protein molecule the nitrogen and carbohydrate leave the body hand in hand. As a rule, the nitrogen loiters behind, greatly to our annoyance in estimating the source of the sugar in the urine. Mendel and Lewis[23] have recently shown that this delay was increased if either indigestible substances or cotton seed oil form a prominent part of the diet—just the sort of foods which our diabetic patients eat. Consequently if an attempt to determine the quantity of carbohydrate from protein (dextrose nitrogen ratio D : N) is made, this irregularity in the excretion of nitrogen must be considered. When one adds to this difficulty that of determining what share the quantity of residual carbohydrate in the body bears to the total sugar excreted, and when one considers that even under an absolutely uniform diet of 1,000 gm. meat and 1,750 c.c. fluid intake for fifteen days Naunyn[24] found variation of sugar excretion from 12 gm. to 43 gm., and frequently of 100 per cent., I feel very modest about asserting that my patients are producing any given quantity of sugar for each gram of nitrogen excreted. Naunyn says that these spontaneous variations may reach even 70 gm. Kulz has emphasized this same point. If under ideal conditions for fifteen days such variations exist, it behooves one to accept with caution reported D : N ratios for a period of a few days as being of value or to base arguments, as is sometimes done, on the D : N ratio of single isolated days selected from a series. In the tables of Rumpf, Allard, Hesse, and some of Lüthje's, D : N ratios are recorded which Professor Lusk and I would feel indicated a far larger per cent. of carbohydrate coming from protein than is actually the case. It is arbitrary selection to pick from these tables all ratios above 3.65 : 1 and say they are wrong and to class the remainder as correct. It is

22. Mandel and Lusk: Deutsch. Arch. f. klin. Med., 1904, lxxxi, 472.
23. Mendel and Lewis: Jour. Biol. Chem., 1913-14, xvi, pp. 19, 37.
24. Naunyn: Des Diabetes Melitus, 1906, p. 183.

furthermore remarkable that with fasting all D:N ratios cease to exist. It is also hard to understood how a patient one day fails to burn the protein of an ox, but the next day burns his own body protein with ease. Fasting diabetics will afford unusual opportunities to study this point. As a rule, the high D:N ratios are found when the nitrogen excretion is high, and it may be that to produce these high ratios large quantities of protein may be required.

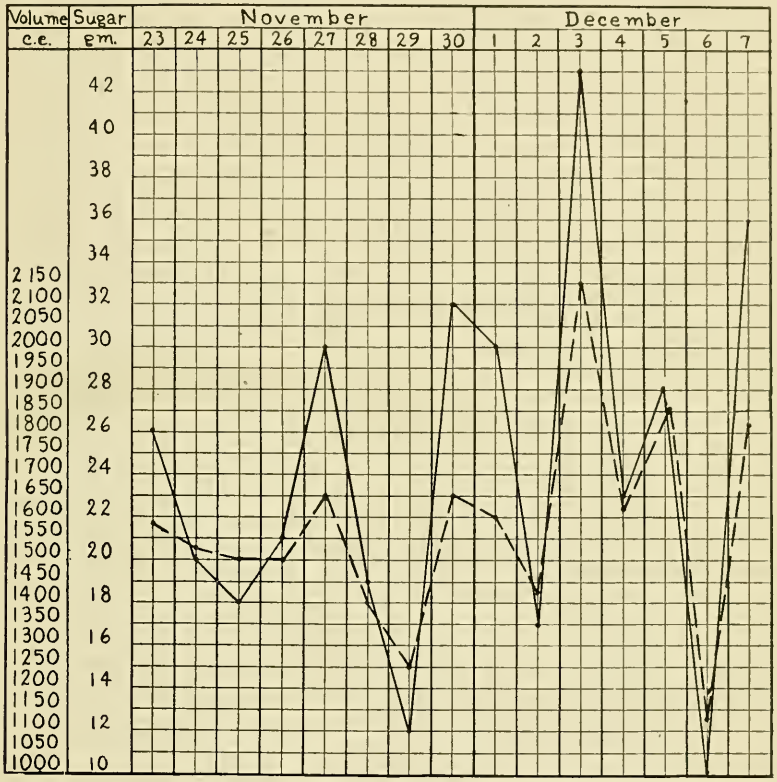


Chart illustrating variations in excretions of urine and sugar of a severe diabetic on a constant diet (from Naunyn). Diet constant 1,000 gm. meat, 1,750 c.c. fluid. Line composed of dots and dashes indicates c.c. urine in twenty-four hours; continuous line, gm. sugar in twenty-four hours.

The small part which the blood plays in the storage of carbohydrate has been pointed out. This is peculiarly unfortunate because one would hope from the percentage of sugar in the blood to derive some knowledge of the course of metabolism in diabetes. As if to emphasize the independence of the metabolism to the content of sugar in the body, I submit at this point Table 6, which gives the respiratory quotients obtained upon individuals whose blood sugar was deter-

mined at the time of the test, reserving discussion of the same to a later portion of the paper.

TABLE 6.—The Blood Sugar and Respiratory Quotient in Severe Diabetes

Case No.	Condition	Per cent. of Sugar in Blood	R. Q.
806	Fasting	0.12	0.71
806	Fasting	0.14	0.68
786	Fasting	0.17	0.69
806	After potato (60 gm. carb.)	0.18	0.69
765	Fasting	0.18	0.74
810	Fasting	0.19	0.72
806	After one egg and 200 gm. vegetables	0.19	0.72
765	Fasting	0.23	0.76
765	Fasting	0.24	0.73
714	Fasting	0.25	0.78
786	After oatmeal (60 gm. carb.)	0.25	0.74
765	After oatmeal (10 gm. carb.) and potato (48 gm. carb.).	0.26	0.74
773	Fasting	0.27	0.70
773	After oatmeal (80 gm. carb.)	0.30	0.70
746	Fasting	0.30	0.70
746	After oatmeal (40-60 gm. carb.)	0.36	0.74
786	After oatmeal (120 ± gm. carb.)	0.36	0.83

IV. THE RESPIRATORY METABOLISM AND ITS RELATION TO THE UTILIZATION OF CARBOHYDRATE

An examination of the composition of the carbohydrate molecule will show that it contains sufficient oxygen to unite with all the hydrogen present. Consequently, for each volume of oxygen used in the oxidation of carbohydrate a volume of carbon dioxid will be produced. The relation which the volume of carbon dioxid produced bears to the oxygen required for the oxidation of a food constitutes its respiratory quotient. It is obvious, therefore, that the respiratory quotient of such a carbohydrate as glucose ($C_6H_{12}O_6$) is 1. It matters not whether the oxidation takes place rapidly outside of the body in a flame, or less obtrusively in the body during twenty-four hours. Protein, on the other hand, does not contain sufficient oxygen for the hydrogen atoms contained in its molecule. As a result, in the burning of protein, oxygen must be used not only for the carbon in the molecule, but for the hydrogen as well. The denominator of the fraction is thus increased, and the respiratory quotient of protein must be less than 1, and is 0.81. The protein molecule is made up of many component parts and while the respiratory quotients of these parts vary greatly, yet for protein as a whole the foregoing quotient, 0.81, holds. With fat a similar condition exists to that in protein, only there is still more hydrogen present to require oxygen, so that the amount of oxygen necessary for the combustion of fat is still greater, and as a result the respiratory quotient falls to 0.70. The respiratory quotient of alcohol is still lower, namely, 0.67. Beta-oxybutyric acid, which can be taken

as the chief one of the group of acid bodies formed in diabetes, has a respiratory quotient of 0.89, diacetic acid has a respiratory quotient of 1.00, and acetone of 0.75, so that one will not go far astray to take 0.89 as a common respiratory quotient for these three acid bodies.

The respiratory quotient of an individual can be determined by measurement of the quantity of carbon dioxid exhaled and the oxygen absorbed. When this is done, information is obtained concerning the character and total amount of the combustion taking place in the body. Since the urinary nitrogen gives us a definite idea of the quantity of protein metabolized, if we calculate what this represents and subtract it from the total material burned, we have left the combustion derived simply from fat and carbohydrate. When the respiratory quotient of fat and carbohydrate, as well as that of the individual, is known, it is possible, by computation, to determine the share which these two variables have taken in the total metabolism.

TABLE 7.—The Respiratory Quotient (R. Q.) of a Food is Obtained by Dividing the Volume of Carbon Dioxid Produced During Its Oxidization by the Volume of Oxygen Absorbed

Volume of Oxygen Absorbed	R. Q.
Carbohydrate: $C_6H_{12}O_6 + 6\ O_2 = 6\ CO_2 + 6\ H_2O$	
Oxygen is required for oxidation of carbon alone	
$\frac{6\ CO_2 \text{ produced}}{6\ O_2 \text{ absorbed}} =$	1.00
Fat: $C_{51}H_{101}O_6$	
Oxygen required for carbon and a large quantity of hydrogen	0.71
Protein: Occupies an intermediate position	0.81
Alcohol: C_2H_6O	0.67
Beta-Oxybutyric acid: $C_4H_8O_3$	0.89
Diacetic acid: $C_4H_6O_3$	1.00
Acetone: C_3H_6O	0.75

The Technic of the Determination of the Exchange of Carbon Dioxid and Oxygen in Man.—Two types of apparatus are employed to learn the exchange of carbon dioxid and oxygen in man; the calorimeter and respiration apparatus. In the closed chamber of the calorimeter the oxygen admitted and the carbon dioxid withdrawn can be accurately determined in periods usually of one hour's duration, but it is better to take the average of the results obtained in three successive periods. Occasionally each period may be shortened to three-quarters of an hour, exceptionally to half an hour, but the large size of the calorimeter increases the chances for error. The calorimeter is cumbersome, expensive to construct and to maintain, and the length of the experiment is not only disagreeable to the patient, but disadvantageous in studying the results of rapid changes in the metabolism, which are desirable in a study of the utilization of foods. On the other hand, the respiratory apparatus is advantageous because the exchange

of gases can be determined during short periods of fifteen minutes. It is disadvantageous, however, because, the periods being so short, errors at the beginning and end of the periods are magnified and because the individual must breathe through a nosepiece or mouthpiece, and this introduces an abnormal state. Unfortunately, in each form of apparatus, the error of a leak falls chiefly on the oxygen, because the patient and the apparatus constitute a closed circuit, and any diminution in gas in this circuit must be offset by the addition of oxygen. A more troublesome source of error and one difficult to avoid arises from the possibility of the patient exhaling carbon dioxid, which has previously accumulated in the body, at a more rapid rate than corresponds with the oxygen inhaled. The patient is said to "pump out" carbon dioxid. There is also another error due to carbon dioxid which is lost by cutaneous respiration, and it has been calculated that this would lower the quotient 0.01 to 0.15.

Many pitfalls, therefore, lurk in the determination of the respiratory exchange of an individual. The carbon dioxid is the more easily estimated of the two gases and in early experiments on metabolism investigators attempted this alone. The determination of oxygen is far more difficult. Hence, in dealing with the respiratory quotient, which depends on the relation of these two determinations to each other, one treads on very dangerous ground, and all statements regarding the respiratory quotient of individuals must be accepted with caution. The general picture of the respiratory quotient in an individual is far more valuable as a guide to his true metabolism if based on several experiments than is the result of a single experiment. Similarly, it is probably safer to average the results of a series of cases than to attach too much importance to figures obtained in one.

The Respiratory Quotient of the Normal Individual.—The respiratory quotient of the normal individual is best determined at least twelve hours after a meal. It has been shown that if this rule is not followed the composition of the meal will have a marked influence on the result. Under these circumstances the respiratory quotient of normal individuals does not greatly vary. Benedict, Emmes, Roth and Smith[25] working at the Nutrition Laboratory of the Carnegie Institution, have studied the basal gaseous metabolism for 89 men and 68 women and their average results are shown in Table 8.

I would call attention to the slight difference existing between the respiratory quotient of men and women—0.83 and 0.81. I have also incorporated the heat production, calculated from the oxygen intake, which was approximately 25 calories per kilogram per twenty-four hours. This latter figure is lower than we are apt to consider, but it

25. Benedict, Emmes, Roth and Smith: Jour. Biol. Chem., 1914, 18, 139.

should be remembered that it is based on fasting periods when the patient is purposely endeavoring to be quiet. It would be absolutely wrong, from such determinations covering periods of fifteen minutes, or even a few hours, to draw conclusions on the total heat production for the day. In illustration of the method and at the same time of the difficulties of determining the respiratory quotient of normal individuals I give the figures in my own case (Table 9).

TABLE 8.—Respiratory Quotient and Total Metabolism of Normal Individuals at Rest at Least Twelve Hours After the Last Meal

Individuals	R. Q.	Calories per Kilo per 24 Hours
89 men	Average = 0.83	25.5
68 women	Average = 0.81	24.9

TABLE 9.—Respiratory Quotient of a Normal Person

Normal individual (E. P. J.) fasting experiment. December 23, 1914. Weight, 64.9 kilos. Height, 177.8 centimeters.

Duration		CO_2 Per Min. c.c.	O_2 Per Min. c.c.	R. Q.	Calories per kilo. per 24 hours
Min.	Sec.				
15	6	152	192	0.80	20.40
14	59	150	194	0.77	20.51
15	0	153	196	0.78	20.77

Average = 0.78

Naturally I took the greatest possible pains to be quiet and breathe in a normal manner, but it will be seen that whereas the values for the carbon dioxid of themselves, and of oxygen for themselves vary to an extremely small degree from period to period, yet they differ sufficiently to make a considerable variation in the respiratory quotient. This experiment emphasizes the possibilities for error in the determination of the respiratory quotient even under most favorable circumstances.

The respiratory quotient of individuals fasting for long periods is well exemplified by the studies made by Benedict[15] on a man who went thirty-one days without food. These are illustrated in Tables 10 and 11.

It will be seen that, prior to the experiment, the respiratory quotient differed little from that of the group of normal individuals above mentioned. With the withdrawal of all food the respiratory quotient fell, and after the fifth day reached a point which Magnus-Levy[26] has said

26. Magnus-Levy: Ztschr. f. klin. Med., 1905, lvi, 83.

theoretically represents the quotient which is obtained when the metabolism consists of 85 per cent. of fat and 15 per cent. of protein, namely, 0.72. In other words, five days of starvation removed the last discernible influence of carbohydrate remaining stored in the body, and the individual lived wholly on body fat and body protein. It is possible to discover how much fat and how much carbohydrate take part in the metabolism.

TABLE 10.—The Respiratory Quotient of a Man During a Prolonged Fast

Period	Time	R. Q.	Calories per Kilogram Body Weight
Preliminary Period	Fourth day before fast	0.81	33
	Third day before fast	0.89	32
	Second day before fast	0.89	29
	First day before fast	0.82	27
Period of Fast	Days 1—5 of fast	0.77 (Avge.)	26
	Days 6—31 of fast	0.72 (Avge.)	23
	Days 6—31, early a. m.	0.73 (Avge.)	23
After Period	Second day after breaking fast*	0.78	25
	Third day after breaking fast*	0.94	27

* Twelve hours after food.

TABLE 11.—Quantities of Protein, Carbohydrate and Fat Oxidized by Fasting Man at Nutrition Laboratory *

Period of Fast	R. Q.		Quantities Oxidized			Calories per kilo. per 24 hours
	Actual	Non-Prot.	Protein gm.	Carb. gm.	Fat gm.	
1st Day	0.78	0.76	43	69	135	30
2d Day	0.75	0.74	50	42	142	30
3d Day	0.74	0.74	68	39	130	29
4th Day	0.75	0.71	71	4	136	28
5th Day	0.76	0.72	63	15	133	28
6th to 31st Day Average	0.72	0.70	53	0†	114	26

* Determined from the Daily Metabolism, the Urinary Nitrogen and the Calculated Non-Protein R. Q.
† Actually a total of 32 gm. carb. were burned during the sixth to thirteenth day, inclusive, and later none.

Knowing the nitrogen in the urine, one can calculate the amount of oxygen employed by the body for the oxidation of the protein[27] which it represents, and correspondingly, the amount of carbon dioxid given off can be determined. If we subtract these computed figures from the total carbon dioxid and oxygen obtained by direct experiment, we have left the carbon dioxid produced by the non-protein metabolism in the body, and the relation of the two gives the non-protein respira-

27. In estimating the quantity of body protein burned from nitrogen in the urine the equivalent 6.00 is employed instead of 6.25.

tory quotient. In a useful table constructed by Lusk,[28] the percentage of carbohydrate and of fat for any given non-protein respiratory quotient between 70 and 100 can be calculated. On this basis it was shown that Benedict's fasting man burned either no carbohydrate or only a trace after the sixth day. When the respiratory quotient of this man was 0.73 on the seventh day it represented a nonprotein respiratory quotient of 0.70 and no carbohydrate was burned. A respiratory quotient of 0.74 gave a nonprotein respiratory quotient of 0.71, which represents the oxidation of 3.8 gm. of carbohydrate; a respiratory quotient of 0.76 gave a nonprotein respiratory quotient of 0.72, which is evidence that 15 gm. carbohydrate were burned.

Respiratory Quotient in Normal Individuals after Food.—The respiratory quotient following the ingestion of food is shown well by the fasting man at the Nutrition Laboratory for the periods before fasting commenced. It will be seen that twelve hours after food it varied from 0.81 to 0.89 in the four days. Similarly, following the termination of the fast, the respiratory quotient rose, indicating the combustion of large quantities of carbohydrate.

An experiment was performed on myself which was comparable to those later carried on with the diabetic patients when tests were made of the influence of food on their metabolism. The changes in my own respiratory quotient following the ingestion of 60 gm. of carbohydrate in the form of oatmeal are given in Table 12.

It will be seen that the respiratory quotient within an hour rose some eight points after eating 60 gm. of carbohydrate in the form of oatmeal. It has been calculated that if 48 gm. carbohydrate are burned in twenty-four hours at the rate of 2 gm. of carbohydrate each hour continuously for the twenty-four hours, the respiratory quotient would rise 3 points—in other words, would be about 0.75 instead of 0.72, which is a fat-protein quotient. I wish to emphasize the change in respiratory quotient of only 3 points when approximately 48 gm. carbohydrate are burned at the rate of 2 gm. carbohydrate per hour per day, and the rise of 8 points following directly on the ingestion of 60 gm. carbohydrate. The continuous combustion of small portions of carbohydrate amounts to the combustion of a considerable quantity of carbohydrate during the whole day, and yet it will raise the respiratory quotient very little. The combustion of 24 gm. of carbohydrate at the rate of 1 gm. per hour could scarcely be detected with our present methods, and yet a tolerance for 24 gm. carbohydrate is relatively a high tolerance when one is dealing with serious cases of diabetes.

The Respiratory Quotient in Diabetes.—In mild cases of diabetes, when the urine is free from sugar and the carbohydrate in the diet

28. Williams, Riche and Lusk: Jour. Biol. Chem., 1912, xii, 357.

large, the respiratory quotient differs little from that of normal individuals. The respiratory quotient of these same mild cases of diabetes will be lowered by fasting or by the withdrawal of carbohydrate, as just shown in the case of the normal fasting man. Undoubtedly the limited quantity of carbohydrate in the diet in cases of severe diabetes is responsible to a large degree for the low respiratory quotient which such patients show. Magnus-Levy called attention to this, and so

TABLE 12.—Metabolism of a Normal Individual After Food
Weight, 64.9 kilos. Height, 177.8 cm.

Date	Condition	CO_2 Per Min. c.c.	O_2 Per Min. c.c.	R. Q.	Calories Per Kilo. Per 24 Hours
9/ 9/14	1-2 hours after breakfast	205	241	0.85	26
9/10/14	1-2 hours after breakfast	192	237	0.81	25
9/30/14	9 a. m., fasting	159	194	0.82	21
	10:30 a. m., after 60 gm. carb. as oatmeal	189	212	0.90	23
12/23/14	8 a. m., fasting	152	194	0.78	21
	1 p. m., fasting	151	196	0.77	21

TABLE 13.—Illustration of Fall in Respiratory Quotient of Mild Diabetic*
Case 714. Female. Aged 38 years, 9 months. Weight 53 kilos.

Date	R. Q.	Urine Sugar	Diet †			
			Carb. gm.	Prot. gm.	Fat gm.	Alcohol gm.
Dec. 3		4.4%	+ +	+ +	+ +	0
Dec. 4- 5		20 gm. ‡	+	+	+	10
Dec. 5- 6	0.78	0	0	0	0	25
Dec. 6- 7	0.75	0	15	40	45	10
Dec. 7- 8	0.75	0	15	45	60	7
Dec. 10-11	0.73	0	15	55	100	9

* Tests were made fasting at 8 a. m., which was one hour after the collection of the twenty-four-hour urine.
† Approximate.
‡ In fourteen hours.

have other observers. It is well exemplified by the change in the respiratory quotient in Case 714. This patient, with only moderate acidosis, became sugar-free on April 16, 1914, following fourteen days of treatment. On Dec. 3, 1914, she reentered the hospital with 4.4 per cent. of sugar, but under fasting treatment became sugar-free after the omission of four meals. The respiratory quotient on successive days is shown in Table 13.

It will be seen that whereas the respiratory quotient was 0.78 on entrance, owing undoubtedly to the oxidation of some of the carbo-

hydrate ingested, though much at the same time was being lost in the urine, this rapidly decreased to 0.73 under starvation followed by a low carbohydrate diet. Yet this could not be considered a severe case of diabetes. The quotient was low simply because the woman was living almost exclusively on a fat protein diet.

The problem of drawing inferences from the respiratory quotient in diabetes is complicated by the fact that much of even the little carbohydrate which is given to a diabetic patient is lost in the urine. The patient really approaches the condition of the fasting man in that he is living exclusively on fat and protein, although in this case not that of his own body. If all the carbohydrate ingested is lost in the urine, his respiratory quotient would be 0.72. But there are other complications. Occasionally cases of diabetes are seen in which the sugar in the urine exceeds that of the diet, and speculation at once arises as to the source of this excess of sugar. Magnus-Levy[26] has pointed out that if the sugar in the urine amounted to 60 gm. and the protein in the diet to 100 gm., the additional quantity of oxygen which would be demanded to form this amount of sugar out of protein would lower the respiratory quotient to 0.70. The situation is still further complicated by the presence of unoxidized acid bodies in the urine, amounting frequently to 20 to 40 gm. and occasionally to 60 gm. calculated as beta-oxybutyric acid. The amount of oxygen consumed in the formation of these bodies—for beta-oxybutyric acid is far richer in oxygen than are protein and fat—would again lower the quotient, and it has been calculated by Magnus-Levy that the respiratory quotient of a diabetic patient presenting 60 gm. of sugar in the urine for 100 gm. of protein in the diet, and excreting 20 gm. of beta-oxybutyric acid, would fall as low as 0.69. For convenience, these figures are summarized. The respiratory quotient of the fasting man at the Nutrition Laboratory was 0.72. The calculated respiratory quotient of a normal individual who is burning 15 per cent. protein and 85 per cent. fat is 0.72. The theoretical respiratory quotient of a diabetic individual excreting all the carbohydrate in the diet, and 60 gm. of glucose for each 100 gm. of protein in the diet, is 0.70. The theoretical respiratory quotient of the diabetic individual excreting 60 gm. glucose for 100 gm. protein and 20 gm. beta-oxybutyric acid as well, is 0.69. These calculations presuppose that the sugar and beta-oxybutyric acid excreted were formed during the same twenty-four hours, but who knows whether this is the case? The theoretical nonprotein respiratory quotient of a case of diabetes living on fat and the noncarbohydrate part of the protein molecule, as calculated by Lusk, is also 0.69.

Table 14 shows the theoretical respiratory quotient, which should be reached under varying conditions of diet for a normal individual,

and the changes which theoretically are present under special conditions in diabetes. Figures of this type have dominated the discussions of the metabolism in diabetes from the start, and whenever experiments have not produced figures comparable with these, they have often been considered erroneous. We are taught to believe that cases of diabetes are not severe unless the respiratory quotient is 0.69. It is questionable, however, whether the experimental data at our disposal enable us to say that our theories are backed up by the results which we obtain. If one looks over the lists of respiratory quotients obtained in successive periods with any variety of respiratory apparatus or calorimeter, he will be shocked at the discrepancy and forced to the belief that any argument based on a change in the respiratory quotient of one point is unjustifiable, and that any argument which is based on a change in the respiratory quotient of two points really hangs on a

TABLE 14.—Theoretical Respiratory Quotients (from Magnus-Levy)

Diet	Calories	R. Q.
Protein, 100 gm. (100 × 4.1 = 410) Carb., 567 gm. (567 × 4.1 = 2325)	2,735	0.97
Protein, 100 gm. (100 × 4.1 = 410) Fat, 250 gm. (250 × 9.3 = 2325)	2,735	0.72
Loss in Urine Sugar, 60 gm. (60 × 4.1 = 246)	2,489	0.70
Loss in Urine Sugar, 60 gm. (60 × 4.1 = 246) B-Oxy. acid, 20 gm. (20 × 4.7 = 94) Total loss = 340	2,395	0.69

very slender thread. A change of three points is, however, deserving of consideration, but modesty should rule in conclusions which are to be drawn from any given set of experiments.

It is appropriate to discuss here what constitutes a severe diabetes. At the outset it can be said for our own encouragement that Naunyn did not pretend to be able to distinguish accurately between the various types. Usually by severe diabetes is understood those cases in which —to quote von Noorden—"notwithsanding a prolonged, extreme carbohydrate-free diet, the urine contains sugar." By an extreme carbohydrate-free diet von Noorden undoubtedly meant one containing protein, fat and a few green vegetables—in other words, a diet with 10 gm. carbohydrate, more or less—not a strictly fat-protein diet. The definition is also open to objection, because one frequently meets with cases of diabetes of long duration in which but a small per cent. of the carbohydrate intake is excreted in the urine, yet this persists for many days on an extreme carbohydrate-free diet, but the case could not be classed as severe.

Another method of classification is adopted by Lusk, who considers cases severe in which, when the patients are put on a protein-fat diet, there is a dextrose-nitrogen ratio of 3.65:1. By this he means that 3.65 gm. of dextrose appear in the urine for 1 gm. of nitrogen, or the 6 gm. of protein which it represents. In other words, 60 per cent. (actually 3.65÷6.25=58.4 per cent.) of the protein burned by the body appears in the urine in the form of sugar. Lusk considers that this is the greatest possible amount of sugar which can appear in the urine on a carbohydrate-free diet, and he assumes that it comes wholly from protein. This conclusion has been reached with many observations on dogs, following injections of phloridzin, and by one case of diabetes coming under his personal observation, and he refers to other cases selected from the literature.

Unfortunately, or perhaps fortunately, neither of these methods of classification at the present time are wholly satisfactory, because, thanks to Dr. Allen, our patients now become sugar-free very readily. It is possible that fasting will not remove the sugar from the urine of all diabetic patients, but this has been my experience with every case when I have followed Dr. Allen's directions, and my experience coincides with that of many others. It may be that recent cases of diabetes have been of a different type from those hitherto encountered, but this is hardly possible. Consequently we cannot adopt the definition of von Noorden, and it is embarrasing to adopt the precise definition of Lusk. The dextrose-nitrogen ratio vanishes with fasting, and the clinician does not wish to expose his patient before beginning fasting to the dangers of a protein-fat diet simply to determine the severity of his case. I am hoping that with the added knowledge of diabetes which the introduction of fasting has brought about, Professor Lusk will pursue his studies further and give us definite rules for testing the severity of the disease. Perhaps definite quantities of protein alone or some special form of protein or derivative of protein could be administered to these patients, and the amount of sugar in the urine determined. Should this method not furnish satisfactory results, another series could be carried out in which varying quantities of fat as well as protein could be added, and if a third factor were necessary, the calories per kilo could be standardized. But we can trust Professor Lusk to give us help. Of course dextrose-nitrogen ratios are of little significance without simultaneous reports of the blood sugar.

In the data which will follow, consideration will be taken of both von Noorden's and Lusk's classification, but also the severity of the cases will be indicated by a statement of the time intervening between the period of observation and death in coma. It would seem as if the severity of the type of diabetes which resulted in death by coma should challenge criticism.

As the periods of observation before death in coma are of importance, the intervals between the determination of the respiratory quotient of the patient and death are given. See Table 16, which will later be discussed more in detail. This appears far more rational than to give the duration of the course of the disease, for many patients present a mild type of diabetes for many years, changing over to a severe type at a comparatively short period before death.

Table 15 summarizes the respiratory quotients of cases of diabetes considered severe by their observers:

TABLE 15.—Respiratory Quotient in Severe Diabetes

Year	Observers	Cases	R. Q.
1894	Weintraud and Laves: Ztschr. f. physiol. Chem., 1894, xix, 603.	1	0.70
1897	Nehring-Schmoll: Ztschr. f. klin. Med., 1897, xiii, 59.	2	0.72
1905	Magnus-Levy: Ztschr. f. klin. Med., 1905, lvi, 86.	2	0.71
1907	Mohr: Ztschr. f. exper. Path. u. Therap., 1907, iv, 910.	1	0.72
1908-1911	Benedict and Joslin: Carnegie Inst. of Washington, Publications 136 and 176, 1910, 1912.	19	0.73
1912	Rolly: Deutsch. Arch. f. klin. Med., 1912, cv, 494.	8	0.74
1912	Grafe and Wolf: Deutsch. Arch. f. klin. Med., 1912, cvii, 201.	3	0.74
1912-1914	Benedict and Joslin, 1914-15.....	7	0.73
		Total 43	Average 0.73

It will be seen that there is surprising unanimity of agreement among the different groups. It should be stated that Leimdorfer[29] has obtained much lower quotients varying between 0.64 and 0.68 with five cases which he considered severe. His figures, however, have not been generally accepted. One of the cases which he considered mild at no time showed a respiratory quotient above 0.70. According to the computations given above from Magnus-Levy, it was shown that, theoretically, in a diabetic patient with 60 gm. of sugar in the urine for each 100 gm. of protein in the diet—in other words, approximately the Lusk dextrose-nitrogen ratio—and with 20 gm. of beta-oxybutyric acid, the respiratory quotient would not go below 0.69, and he further points out that, in order for the ratio to sink to 0.653, 150 gm. of sugar must be formed from 150 gm. of protein, and 40 gm. of beta-oxybutyric acid must appear in the urine when the patient is on a diet of 150 gm. protein and 250 gm. fat. A respiratory quotient of 0.653 is a figure so low that it should be entertained with scepticism. The average respiratory quotient of 0.73 for forty-three cases of diabetes clinically considered severe is a far safer figure to follow than

29. Leimdorfer: Bio-Chem. Ztschr., 1912, xl, 326.

to pick out one, two or three from the forty-three cases and say that these represent severe cases of diabetes and the others do not. The errors of the determinations of the quotients are so great that the average figures are safer than the individual ones. These respiratory quotients, as Grafe and Wolf[30] pointed out, show that at least some carbohydrates were being oxidized by severe diabetic patients. They also pointed out that with the improvement of patients the respiratory quotients increased from 0.743 to 0.817 in a fasting condition.

These figures suggest at the first glance that very little carbohydrate was burned in this group of severe cases of diabetes. The respiratory quotients are identical with the quotients obtained under similar conditions with the fasting man at the Nutrition Laboratory, though his average for the whole day for the fasting period was 0.72. But we must remember that two corrections are to be made in these figures; first, sugar has been lost in the urine which has been formed from protein, and second, there have been varying amounts of beta-oxybutyric acid, diacetic acid and acetone excreted. Both of these processes represent processes of oxidation and by demanding additional oxygen for which no carbon dioxid is produced tend to lower the respiratory quotient. Therefore, if we grant that the series represents cases of severe diabetes, we must reach the conclusion that these diabetic patients utilized some carbohydrate, and that their respiratory quotients would have been several points above 0.73, had they not been lowered to 0.73 by the production of sugar from protein and the formation of acid bodies.

Are the cases reported in Table 15 severe? At least no cases of greater severity have been hitherto published. By von Noorden's criterion they might be considered severe, for they did not become sugar-free with restricted diet, yet it is true that this restricted diet was not so rigid as is often employed on account of the marked acidosis. If we accept Lusk's criterion (and I am not ready to do so until a second human case is studied under modern conditions[31]) they were not severe. Not one of Benedict's and my cases showed a persistent D:N ratio of 3.65:1. Yet the clinical facts point to severity. In the first group of nineteen cases of diabetes reported in 1908-1912 by Benedict and myself, eighteen patients are dead and of these fifteen

30. Grafe and Wolf: Deutsch. Arch. f. klin. Med., 1912, cvii, 201.

31. By modern conditions I mean (1) exclusive fat-protein diet, (2) under surroundings which make errors in diet impossible, (3) a duration of at least seven days to exclude the washing out of stored carbohydrate, (4) a constant (not falling) D:N ratio of 3.65:1 for the last three of the seven days, and (5) several daily blood sugar determinations to furnish some proof, inadequate though it be, that the sugar in the urine has not come from that left over in the blood. At present I cannot advocate such a test because of the danger of acidosis, and believe it better to leave the question in this form, undecided.

died in coma. This fact can be taken as a measure of their severity. I do not believe, however, that this alone justified us in saying that a case of diabetes is of the severest type. I conceive it possible, for a moderately severe case of diabetes, by sudden changes of diet, to be driven into coma accidentally. This was done years ago, when diabetic patients who were living on a free diet on coming to the hospital were suddenly deprived of carbohydrate and the fat and protein were increased. It appears to me quite probable that most cases of coma in diabetes have occurred long before the disease had reached its greatest severity, and I wish to point out that therein lies great hope for the future.

It will be of interest, however, to note the respiratory quotient of a group of six cases of diabetes all ending in coma, death occurring within a period of 44 to 14 days from the time of observation, and to compare these with a group of patients whose respiratory quotient was observed at a greater interval from death by coma. This is shown by Table 16.

TABLE 16.—Respiratory Quotient in Severe Diabetes: Comparison of Fatal Cases and Cases of Living Patients

Fatal Cases			Living Patients		
No. of Cases	Days Before Coma	R. Q.	Case No.	Days Before* March 1, '15	R. Q.
6	44-14	0.71	552	801	0.72
8	442-70	0.74	765	125	0.73
			786	111	0.71
			806	72	0.70
			4 Cases	801-72	0.715

* All of these patients were in good condition May 1, 1915, which would add sixty-two days to the duration since the observations were made.

A consideration of this table suggests that with approaching death the respiratory quotient falls. It will be seen that the cases ending fatally within a period of from 44 to 14 days from the time of observation, gave a quotient of 0.71, as contrasted with a quotient of 0.74 in cases terminating fatally in coma at an interval from death of from 442 to 70 days. If we had these figures alone, the inference might be justified, but caution is necessary before drawing such a conclusion. Four living diabetic patients show a respiratory quotient almost as low—0.715. Instead of progression toward death by coma, their general condition has improved. In other words, a falling respiratory quotient does not necessarily mean approaching death by coma. It does mean that these patients have lived for prolonged periods on an almost exclusively fat-protein diet and suggests that they are forming carbohydrate out of protein and producing acid bodies.

It should be said that all of these living patients have been treated either by much restricted diets or by fasting as advocated by Dr. Allen. When they were first seen the cases appeared to be quite as severe as those earlier studied which ended fatally in coma. What shall we say of them at present? None of these patients can be considered well, but all lead a comfortable life at home.

The group of patients dying within a period of from forty-four to fourteen days deserves further comment. The average quotient of these cases was 0.71. From four of these the non-protein respiratory quotient has been reckoned, and it amounted to 0.695. This respiratory quotient implies that much material must have been formed in the course of the metabolism which used a portion of the oxygen. This was especially true of Case 246, in which there was a respiratory quotient of 0.69, which was based on an average of twenty-nine periods, most of which were fasting.[32] Stimulated by inquiries from Professor Lusk, I am fortunately able to show the cause of the particularly low quotient in this patient. His diet and urinary analyses will be found in Tables 17 and 18. The average daily urinary nitrogen for the six days of observation was 16.6 gm., and it was considered that this represented approximately the metabolism of 100 gm. protein. The beta-oxybutyric acid was 46.6 gm. daily and allowing for acetone and diacetic acid the total excretion of acid bodies was assumed to be 60 gm. The fat in the diet as originally recorded was probably inaccurate, and I believe 165 gm. daily near to the exact quantity. From these tables it will be seen that the daily carbohydrate in the diet was 71 gm., and the dextrose excreted was 102 gm. giving a minus balance of 31 gm. This, with the 16.6 gm. nitrogen in the urine, gives a D : N ration of only 1.9 to 1. In Table 18 are placed the data from which the respiratory quotient can be calculated from the diet and urine, and they show that after deductions for dextrose and acetone bodies, the theoretical quotient would be 0.692, which it will be remembered was identical with the respiratory quotient found by experiment. These tables are submitted as proof that a quotient of 0.69 does not necessarily mean that the capacity for burning carbohydrate has been totally abolished.

Computations of a similar character by Grafe and Wolf[30] lead to the same conclusion.

According to these writers, "the conception which on the whole appears to have the greatest probability is that even the severest diabetic has at his disposal 20 to 30 gm. of glycogen for combustion or synthesis, thirteen to twenty hours after a meal containing a minimal

32. Benedict and Joslin: Metabolism in Diabetes, Pub. Carnegie Institution of Washington, 1910, No. 136, p. 68.

amount of carbohydrate. Perhaps the complete loss of the power of combustion of sugar is, broadly speaking, no longer consistent with life."

TABLE 17.—Metabolism in a Case of Severe Diabetes with a Respiratory Quotient of 0.69 *

Case C., No. 246. Male. Acute onset at 28. Death in coma in fifteen months.

Day	Urine					Diet				Sodium Bicarb. Gm.
	Volume, c.c.	N, Gm.	NH_3 Gm.	B-oxy., Gm.	Dextrose, Gm.	Carb., Gm.	Prot., Gm.	Fat, Gm.	Alcohol, Gm.	
1	2,935	16.3	4.8	29	72	15	13	55	15	0
2	3,710	13.3	5.0	34	106	98	22	225	30	0
3	4,370	19.6	5.5	61	134	65	100	200	30	60
4	4,035	19.4	5.4	61	107	65	100	200	30	60
5	3,330	14.7	5.6	46	100	125	45	100	30	25
6	3,765	16.3	5.0	48	93	65	100	200	22	25
Ave.	3,691	16.6	5.2	46.6	102	71	65	165	26	28

*Daily protein metabolism estimated at 100 gm. Total acetone bodies estimated at 60 gm.
Carbohydrate in diet, 71 gm.
Dextrose in urine, 102 gm.
Carbohydrate balance, 31 gm.
D : N ratio, 1.9 : 1.0.

TABLE 18.—To Supplement Table 17 *

Case C., No. 246.

Diet	Gm.			Calories	O_2 Liters	CO_2 Liters	R. Q.
Protein	100	× 4.1	=	410	96.6	78.2	
Fat	165	× 9.3	=	1535	333.1	235.5	
Carbohydrate	71	× 4.1	=	291	58.9	58.9	
Alcohol	26	× 7	=	182	37.9	25.3	
				2418	526.5	397.9	0.756
Lost in Urine							
Dextrose	102	× 3.7	=	337	76.1	76.1	
Acetone bodies as B-oxyb.	60	× 4.5	=	243	58.1	51.6	
				620	134.2	127.7	
				1798	392.3	270.2	0.692

* The respiratory quotient found, based on an average of 29 periods, chiefly fasting was 0.69.

Effect of Food on Utilization of Carbohydrates in Severe Diabetes.—A moderate number of experiments on the effect of food on severe diabetics has been recorded, but the actual number of experiments to determine the effect of carbohydrate on the respiratory metabolism is very limited. Such experiments have been published by Leo,[33] who

33. Leo: Ztschr. f. Klin. Med., 1891, xix, 101.

considered that the respiratory quotient did increase in two cases of severe diabetes, although this was not uniformly the rule and he concludes that even in severe diabetes a part of the sugar ingested or formed in the body is utilized.

Nehring and Schmoll[34] tested the effect of carbohydrates also in two severe cases of diabetes, but were unable in either to show an increase in the respiratory quotient. Frequently a fall instead of a rise in the quotient took place. Benedict and Joslin,[35] in a series of experiments chiefly with bread and dextrose, state that "the ingestion of carbohydrate produced no very material alteration in the metabolism as a whole," and later "no evidence can be found of a combustion of carbohydrate . . ." Two years later a series of experiments with oatmeal and levulose were reported, but without comment.[36]

Rolly,[37] in a series of experiments, tested the comparative effects of oats, rye, wheat, lentils and green cornmeal on diabetic patients. Unfortunately, few of the experiments were preceded by control periods. Two of his cases he considers severe. In Case 1, at three, five and six hours after 70 gm. of oatmeal were administered, the respiratory quotient was 0.73. After 70 gm. of wheat meal it was 0.76. The respiratory quotient of his Case V after 80 gm. of oatmeal was 0.71, after 80 gm. of rye meal was 0.73, and after 80 gm. of wheat meal was 0.71. Two of his other cases were only moderately severe, and the other only a light case, and all showed an increase in the respiratory quotient after their meals reaching up to 0.83, 0.85 and 0.84 respectively. It will be noted, furthermore, that of the two severe cases, in the first the quotient following administration of wheat meal which was given after oatmeal reached 0.76.

Roth[38] records slight increase of the respiratory quotient following the administration of carbohydrate. The experiments, however, lose much of their value because of the absence of fasting controls on the day the carbohydrates were given.

Falta[19] has mentioned several experiments designed to show the effect of the oatmeal cure on the respiratory quotient. The data of the experiments are not given, but he states that with one moderately severe diabetic the respiratory quotient rose only on the third day of an oatmeal cure, in which 400 gm. had been given daily. Despite this

34. Nehring and Schmoll: Ztschr. f. klin. Med., 1897, xxxi, 59.

35. Benedict and Joslin: Loc. cit. (Note 32) p. 215.

36. Schilling: Inaug. Dissert., Leipzig, 1911, tested the effects of various meals on the respiratory quotient of one severe, one mild and two moderately severe cases of diabetes, and demonstrated no specificity for oatmeal. With the severe case the results were inconstant, but usually tended to show a slight increase in the respiratory quotient.

37. Rolly: Deutsch. Arch. f. klin. Med., 1912, cv, 494.

38. Roth: Wien. klin. Wchnschr., 1912, xlvii, 1864.

enormous quantity of oatmeal, no glycosuria was observed. It is unfortunate that I have not been able to find a later publication which was promised. He furthermore makes the interesting statement, which is so remarkable as to invite confirmation, that a similar result was encountered with a normal individual, whose carbohydrate depots had been robbed by living on a diet poor in carbohydrates for a long time. It would appear that only after these depleted carbohydrate stores were replenished, did the normal individual, like the diabetic, begin to burn carbohydrate. His results are in striking contrast to the changes in respiratory quotient which were shown by the fasting man at the Nutrition Laboratory. At the end of his fast of thirty-one days he ate food almost exclusively in the form of carbohydrate and the quotient promptly rose to 0.79 and 0.96 on the second and third days respectively, emphasizing the fact that in a mixed diet carbohydrates are burned much earlier. He further states that on a meat diet or on a diet with a moderate amount of carbohydrate the diabetic patient seldom shows a quotient above 0.74, and he also noted the fact, to which attention has been called by Nehring and Schmoll, and which is also borne out by our own series of cases, that following the administration of carbohydrate a considerable quantity of carbohydrate not only remains in the body, but the respiratory quotient remains low. Intravenous injections of sugar (30 gm.) given by Falta to severe diabetics, who had eaten 300 gm. of oatmeal for three days without glycosuria, brought about an evident glycosuria, but the respiratory quotient rose proportionately little. In the case of a severe diabetic there was no increase, but a still further lowering of the already low respiratory quotient.

The present series of experiments with foods which I have to report represent a part of the experiments on diabetics whose metabolism following the administration of food was studied at the Nutrition Laboratory since 1910.

Three experiments have been conducted with levulose. In Case 332 100 gm. of levulose were administered when the patient was fasting. This patient was a severe diabetic, weight 40 kg., in the twenty-fourth month of her illness, and died five months later. The respiratory quotient before the levulose was administered was 0.72, and following the levulose the quotient was determined in six different periods during the following three hours and showed an average of 0.69. Despite the fall in the respiratory quotient, the total metabolism increased markedly, although apparently most of the levulose was excreted in the urine. Unfortunately, it is impossible to state how much of the 120 gm. of sugar in the urine for this twenty-four hours came from the levulose and how much from carbohydrates of the preceding day.

Our records indicate that the patient was on a diet containing approximately 100 gm. of carbohydrate. This fact is of interest in comparison with the next two cases, in which also levulose was given.

TABLE 19.—Effect of Levulose on a Severe Diabetic

Case 332. Female. Aged 37 years. Weight 40 kilos.

Date	Condition	CO_2 Per Min.	O_2 Per Min.	R. Q.	Calories per Kilo. per 24 Hours
3/31/11	Fasting	c.c.	c.c.		
10:50	Fasting	151	205	0.74	35
11:23	Fasting	145	211	0.69	36
	100 gm. levulose				
12:16		172	271	0.63	46
12:44		184	261	0.70	44
1:30		180	246	0.73	42
2:05		172	235	0.73	40
2:28		171	250	0.68	42
2:53		166	240	0.69	40
4/2/11					
8:17	Fasting	148	199	0.75	34
8:45	Fasting	151	203	0.74	35
9:14	Fasting	154	213	0.72	36
	Oatmeal = 70 ± gm. carb., 38 gm. butter				
10:13		163	234	0.70	39
10:39		167	228	0.73	39
11:08		177	238	0.75	40
12:12		170	230	0.74	39
1:28		154	206	0.75	35
2:37		163	209	0.78	36

TABLE 20.—Effect of Levulose on Respiratory Quotient of Diabetic Patients

Case	Duration, Months	Month Observed	Carbohyd. Preceding Day, Gm.	Levulose, Gm.	Sugar in Urine 24 Hours, Gm.	R. Q.	
						Before	After
332	Dead 28	23	100±	100	120	0.72	0.69
552	Alive 32	18	30	100	3	0.72	0.76
785	23	20	20	81*	7	No increase	

*81 gm. levulose and later
9 gm. carb. as vegetables
90 gm. total.

In Case 552 also 100 gm. of levulose was administered, but this was given after a prolonged period of low carbohydrate feeding. On the day previous to the experiment the carbohydrates in the diet amounted to 30 gm. The quantity of sugar in the urine in this case during the twenty-four hours of the experiment was 3 gm. The

respiratory quotient rose 4 points, namely, from 0.72 to 0.76 after the levulose.

The third case, No. 785 (Table 20), was that of a boy, aged 16, with severe diabetes of twenty months' duration, weight 42 kg. He had been made sugar-free by prolonged fasting and had been kept on a diet low in carbohydrate and protein, as well as fat. During the twenty-four hours of the test, the urine contained but 7 gm. of sugar. Notwithstanding this fact, the respiratory quotient showed no increase, but a fall of 2 points. The actual figures are not published now, but the comparative values may be considered trustworthy. The evidence in these three cases, therefore, points to no utilization of the levulose in two of the cases. In one of these most of the levulose was probably excreted, but in the other only a negligible quantity. In the third case

TABLE 21.—Effect of Potato on Respiratory Quotient in Severe Diabetes

Case Number	Duration Months	Month Observed	Carbohydrate Intake		Sugar in Urine 24 Hours, Gm.	R. Q.	
			Preceding Day, Gm.	Test Day, Gm.		Before	After
765	7	3	15	63* 22 85	29	0.74	0.73
806	6	3	10	60† 6 66	3	0.68	0.71

* 48 gm. carb. as potato
10 gm. carb. as oatmeal } 63 gm.
5 gm. carb. as cream
Also 1 egg and 30 gm. butter. Later in day, 22 gm. carb. as potato and vegetables

† 60 gm. carb. as potato. Later in day, 1 egg, butter, 6 gm. carb. as vegetables.

there was an increase of three points in the respiratory quotient, indicating a slight utilization of the levulose and there was no excretion of levulose of account.

It was possible to determine the effect of the administration of potato in two cases. In the first case the experiment was complicated in that the patient was given a small quantity of oatmeal at the start, which, however, was stopped on account of her dislike to it, and potato was substituted. In this case, No. 765, no change in the respiratory quotient took place, but in the second, Case 806, a slight increase was noted, and apparently rather more than would be accounted for by the limits of error.

Eleven experiments have been carried out on cases of severe diabetes with oatmeal. These were arranged in some cases to determine the immediate effect of the administration of oatmeal, and in other cases to determine the effect of the prolonged administration of

TABLE 22.—Effect of Potato on the Respiratory Quotient of a Severe Case of Diabetes

Case 806. Male. Weight 62 kilos.

Date 12/22/14	Condition	CO_2 per Min., c.c.	O_2 per Min., c.c.	R. Q.		Cals. per Kilo per 24 Hrs.		Blood Sugar Per Cent.
9:25		156	223	0.70		24		
9:54	Fasting.....	150	224	0.67	0.68	24	24	
10:22		155	228	0.68		25		
10:45		...	...					0.14
	Potato = 60 gm. carb.							
10:55		...	...					0.18
11:59		181	257	0.71		28		
12:22		168	252	0.67	0.69	27	27	
12:55		172	250	0.69		27		
3:00		170	233	0.73		26		
3:26		157	227	0.70	0.72	25	25	
3:54		166	231	0.72		25		
4:45		...	...					0.19

TABLE 23.—Effect of Oatmeal on the Respiratory Quotient of a Severe Diabetic

Case 773. Female. Weight 40 kilos.

Date	Condition	CO_2 per Min., c.c.	O_2 per Min., c.c.	R. Q.	Cals. per Kilo per 24 Hrs.	Blood Sugar Per Cent.
10/10/14 8:00	Fasting.....	146	212	0.69	36	
	Oatmeal = 42 gm. carb.					
11:00		178	249	0.72	43	
10/13/14 8.00	Fasting.....	138	189	0.73	33	0.32
11:00		...	...			0.27
10/19/14 9:00	Fasting.....	135	195	0.70	34	0.27
	Oatmeal = 80 gm. carb.					
12:00		167	237	0.70	40	0.30
10/20/14	After breakfast....	...	...			0.34

Diet contained 15 gm. carb. October 9 and October 18.

TABLE 24.—Effect of Oatmeal on the Respiratory Quotient of Severe Diabetics

Case No.	Duration		Date	Carbohydrates Ignited		Respiratory Quotient		Sugar in Urine, Gm.	Carb. Intake, Gm.	Carb. Balance, Gm.
	Onset to Coma, Months	Month of Test		Day Preceding, Gm.	Before Test Gm.	Fasting	After Oatmeal			
194	34	31	9/22	15	...	0.74		42	15	—27
			9/23	15	190+	0.71	0.71	50	165	+115
			9/24	165	...	0.72*		19	15	—4
246	15	11	8/ 9	50	46	0.71	0.67	124	?	?
		13	10/29	65	60	0.68	0.70	100	125	+25
			10/30	125	...	0.71*		93	65	—28
			10/25-31	71	...	0.69		102	72	—30
281	19	17	12/ 1	15	...	0.75		69	135	+66
			12/ 2	135	29		0.76*	58	45	—13
			12/ 3	45	0	0.76		38	30	—8
332	28	13	5/19	100	25±		0.73	15 in 3 hrs.		
			5/26	95	...	0.73		3 in 3 hrs.		
		24	4/ 2	?	52	0.74	0.74	97		
		26	6/ 2	?	48	0.71	0.69	36		
336	132	127	5/18	20	...	0.73		26	45	+19
			5/21	45	25		0.75	31	45	+14
441	11	9	9/29	15	75	0.70	0.71	65	165	+100
		10	10/ 9	15	73		0.69	?	79	
561	33	23	2/ 7	60	...	0.75		31.1	60	+30
			2/ 8	60	116	0.71	0.74	128.4	185	+57
			2/ 9	185	200	0.72*	0.72*	209.3	205	—4
			2/10	200	...	0.76†		101.86	60	—42
591	50	44	4/10	?	...	0.74		63	30	—33
			4/11	30	...	0.73		37	15	—22
			4/12	15	80	0.70	0.70	85	165	+80
			4/13	165	80	0.73*	0.69*	77	165	+88
			4/15	40	...	0.69		29	?	
773	20	18	10/ 8	115	70		0.70	175.6	165	—10
			10/10	15	47	0.69	0.72	95.4	130	+35
			10/13	50	...	0.73		83.97	50	—34
			10/19	15	80	0.70	0.70	96.50	115	+18
746	22‡	18	10/ 7	65	28		0.73	93.11	65	—28
			10/ 9	15	50	0.73	0.71	86.69	163	+76
			10/10	165	...	0.72*		34.88	25	—10
			10/15	165	80		0.74†	96.28	165	+69
786	17‡	14	11/12	15	60	0.69	0.73	0	62	+62

* R. Q. taken following an oatmeal day.
† R. Q. taken subsequent to two oatmeal days.
‡ Prior to March, 1915.

oatmeal. It will be seen from a study of the tables that as a rule the respiratory quotient remained stationary or fell; in one case it rose 4 points, and in two other cases it rose one point. It will be noted further that the respiratory quotient, when taken fasting on the morning following an oatmeal day, amounted in three cases to 0.73, 0.72 and 0.73 respectively, and that on the morning following a second oatmeal day it was 0.69 and 0.76. The respiratory quotient was also determined in three experiments after the administration of carbohydrate and on the second day it was 0.72. If one looks at the table as a whole, it will be seen that little change in the respiratory quotient took place: in fact, none of any account except on the morning following the second oatmeal day.

The sum total of the results following the feeding of levulose, potato and oatmeal to severe diabetics affords little evidence, from the respiratory quotient, that the carbohydrate was burned, save in the case of one of the experiments with levulose, one with potato, and one with oatmeal. There results correspond closely with what has been recorded in the literature. Personally, I believe that before a final decision on this point can be reached from this particular line of study, further experiments must be performed.

Unfortunately in the experiments recorded no stated agreement was noted between changes in respiratory quotient and variations in the quantity of blood sugar. From Table 6 it is evident that there is a general tendency for the respiratory quotient to rise with an increase in blood sugar, but this may be accidental. Studies now in progress will soon throw light on this phase of the question.

V. ACIDOSIS AS A MEASURE OF THE UTILIZATION OF CARBOHYDRATES

It has been generally accepted that acidosis will appear when carbohydrate food is either withdrawn from the diet or excreted in the urine. It has been unquestionably the universal clinical experience that the patient who excretes quantities of sugar in the urine equal to or in excess of that in the diet exhibits acidosis, and that patients do not show acidosis who are able to utilize approximately 70 gm. of carbohydrate, or large quantities of protein from which carbohydrate may be formed. This statement cannot be so unqualifiedly made, because I have under observation a woman who in her sixth month of pregnancy showed over 6 per cent. of sugar, and later under a careful diet became sugar-free, acquired a tolerance for approximately 100 gm. of carbohydrate, and yet a slight acidosis persisted. Nevertheless, the general mass of evidence points to the disappearance of acidosis when carbohydrates are burned, and on this general concept arguments have been based for and against the utilization of carbohydrate in severe diabetes.

During von Noorden's oatmeal treatment a considerable quantity of carbohydrate ingested is usually retained or burned in the body, and the decrease of acidosis at the same time is usually considered evidence of the latter supposition being correct, but occasionally the acidosis persists although the carbohydrates are not excreted. I doubt if we are in a position to accurately explain the disappearance or non-disappearance of acidosis under these conditions. Oatmeal and other carbohydrates are better retained in the body following starvation, and it is quite possible that a mechanical retention of acid bodies goes hand in hand with the retention of carbohydrate. Magnus-Levy pointed out long ago that these were seldom excreted in concentration of more than 1.5 per cent., and that the fall in acidosis during an oatmeal cure may be simply apparent, because the volume of urine excreted has diminished. The influence of preceding fasting is also important, because this undoubtedly regulates to some extent the storage of carbohydrate. Despite these possibilities, which lessen any argument for combustion of carbohydrate based on the decrease of acidosis following the ingestion of carbohydrate, the slight amount of acidosis which is usually found when diabetic patients are on a full carbohydrate diet points strongly to the view that some carbohydrate is burned. The increase in respiratory quotient on the last days of an oatmeal cure, which Falta observed and we also have noted, is conformatory to this position.

Various writers have observed that the acidosis in diabetics decreases on a vegetable day or fasting day, but it remained for Allen to demonstrate conclusively the remarkable fact that acidosis vanished in practically all severe cases of diabetes under these conditions, and that in the remainder, if carbohydrates to a moderate extent are allowed temporarily the acidosis wholly clears up. If a normal individual fasts, it has been the universal experience of observers that acidosis appears. In other words, the normal fasting individual corresponds with the concept that when carbohydrates are withdrawn from the diet (and this implies carbohydrates which might be formed from protein) acidosis appears. Thus, in the fasting man at the Nutrition Laboratory, acidosis appeared on the second day and continued until the fast was terminated. How can we reconcile the apparent contradiction in the fact that fasting, which dissipates acidosis in diabetes, produces it in normal individuals? Must the prevalent conception be given up that carbohydrate oxidation and acidosis are unrelated and must we acknowledge that here is an instance where the absence of the burning of carbohydrates does not lead to acidosis? Such a conclusion appeared unavoidable until observations at the Nutrition Laboratory on severe diabetics during prolonged fasting began to accumu-

late, showing that whereas at the beginning of the fast the respiratory quotient was the ordinary respiratory quotient of severe diabetes, 0.72, with a continuance of the fast this had a tendency to rise several points, occasionally even to the neighborhood of 0.80. Later experiments, as yet unpublished, at the Russell Sage Laboratory made under the direction of Dr. DuBois and Professor Lusk on one of Dr. Allen's patients suggested a similar condition. In other words, whereas the normal individual showing acidosis exhibits a respiratory quotient based on the combustion of protein and fat alone, the severely affected diabetic during fasting shows a respiratory quotient which could be accounted for only by the combustion of notable quantities of material other than fat and protein. That this material was not protein was evident, because the amounts of nitrogen in the urine excreted during these periods were not abnormal. This increase in the respiratory quotient furnishes the explanation of the fact that the severely affected diabetic in contradistinction to the normal individual, shows no acidosis during a fast.

Several explanations for this increase in the respiratory quotient of fasting diabetics are available. During fasting the diabetic may be able to draw on sources of carbohydrate in the body which the normal individual cannot. Furthermore, the diabetic has in the body undoubtedly more carbohydrate stored than we have hitherto supposed, and the supposition must be entertained that the diabetic really may actually have more carbohydrate in some form in the body than exists in the normal individual. A third supposition for the increase in the respiratory quotient is that considerable quantities of acid bodies have accumulated and that with the improvement of the condition of the patient during fasting these are burned. It will be remembered that beta-oxybutyric acid, diacetic acid and acetone all have relatively high respiratory quotients, namely, 0.89, 1.00 and 0.75 respectively, and therefore the oxidation of a small quantity of these substances would markedly raise the respiratory quotient. Which of these suppositions is correct will be eventually known because of the improved methods of estimating carbohydrate and acid bodies in the blood, fluids and tissues of the body,[39] and also by the help which is afforded from the estimation of the carbon dioxid tension of the blood.

I should like to point out this further possibility: During prolonged fasting, acidosis tends to disappear, in part because the sources of the acid bodies, save for body fat and protein, have been eliminated. So soon as acidosis begins to decrease, there is, as we and others have found, a lessening of the total metabolism, and with this lessening of total metabolism an improvement in the combustion of carbohydrate

39. Marriott: Jour. Am. Med. Assn., 1914, lxiii, 397.

takes place. This in turn favors the combustion of acid bodies. It might well be that the first step to take in the treatment of a case of diabetes is to abolish acidosis completely.

All may be ready to concede that all diabetic patients under fasting conditions are burning carbohydrates, but some may say that the character of the disease has changed, and instead of being a severe type of diabetes the case has become one of moderate severity. Such a criticism is hard to answer. It presupposes, however, that an individual can readily change in the space of a few hours from a state in which death is imminent to one of safety, and that so fundamental a function as the loss of power to utilize carbohydrates can be quickly regained. This would be a remarkable phenomenon. Against this explanation also is the fact that many who have employed fasting treatment with severe cases of diabetes have regretfully acknowledged that either very slight or no increase of tolerance for carbohydrates has been produced in these patients. This would make it still more unlikely that the diabetic patient by fasting altered his nature. It would rather point to the view that the diabetic condition remained unchanged, but that during fasting the diabetic was able to secure and burn material which under other conditions he could not reach, and which the normal individual could not secure.

In conclusion it is gratifying to be able to record that the recent experimental evidence confirms the old clinical view that the severe diabetic still retains power to utilize a portion of the carbohydrate of his diet, small though it may be and that herein lies renewed hope for the success of treatment.

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